6.2000

TABU

LÄÄKEINFORMAATIOTA LÄÄKELAITOKSELTA

LÄKEMEDELSINFORMATION FRÅN LÄKEMEDELSVERKET, FINLAND | DRUG INFORMATION FROM THE NATIONAL AGENCY FOR MEDICINES, FINLAND

6.2000
8. vuosikerta
8 årgången
8th Annual volume

Sammandrag

Summary

*Lehden artikkelien otsikot löytyvät aiheittain ryhmiteltynä Lääkelaitoksen kotisivulta **www.nam.fi** kohdassa Julkaisut – TABU. Hakemistossa ovat mukana artikkelit ensimmäisestä numerosta (1.93) lähtien. Vuoden 2000 numerot löytyvät kotisivuilta pdf-muodossa.*

Summary

Maija Perho
Minister for Social Affairs and Health

Editorial

Health care and the policy on pharmaceuticals

The changing age structure of the population, the rapid developments of the pharmaceutical industry, and rising medicine costs necessitate a review of the Finnish policy on medicines, including the drug reimbursement system, in light of new knowledge.

In its present form, our health care services are totally dependent on medicines, which are the most frequent means of treating illnesses and symptoms. Medicines do, however, constitute only one of many cost items adding up to the sum total of health care expenditure. While health care services fall predominantly within the sphere of the public sector, the pharmaceutical sector consists mainly of private business. Subvention by the society does play a significant role through reimbursing medicine costs attributable to out-patient care and hospitals or other institutions of care.

Although there are many professional and business interest groups in the pharmaceutical sector, their common objective is to provide the best available medical therapy for the patient. The views on the best means to achieve that objective differ, however, as far as drug prescribing, distribution, financing and reimbursement systems are concerned.

Despite pressure from multiple sources, we must ensure that individual interests will not threaten the society's main objectives under its policy on medicine. These objectives include the efficacy, safety and quality of the best medicines for the patient. While its important to create favourable conditions for developing new medicines, it is also essential to ensure that medicines are available at the same prices nationally and regionally. Furthermore, it is important to boost the provision of non-commercial drug information on medicines both qualitatively and quantitatively.

Drug reimbursement shall be at a reasonable level compared with those applicable in countries similar to Finland. To curb costs, the potential to make use of generic products should be investigated in order to reserve funds to reimburse more expensive new medicines.

Any reform of the sickness insurance scheme should be based on the principle that the system guarantees an equal opportunity for everyone to comply with the drug therapy prescribed by the physician, regardless of the patient's financial position. The pricing and special reimbursement systems in respect of medicines shall be understandable, just and fair to the patient, while treating service providers equally and being administratively uncomplicated and logical. Decision shall be objective and based on verifiable criteria.

The reimbursement system should not be unduly complicated, the aim being to achieve maximum health benefits at reasonable costs. Various reimbursement models should be considered, for instance whether it is feasible to pay small sums in reimbursement, or should the reimbursement classes be reduced from three to two. It can also be asked, whether the prescribing practices of physicians could be changed by other than the previously tried means of issuing regulations or instructions.

In spite of the fact that costs will continue to rise in the future, Finland should, as a Nordic welfare state, be able to provide high quality medical therapy and health care in general. The working group appointed by the Ministry of Social Affairs and Health to consider the need for reform of the system of reimbursing medicine costs, is due to give its report on 31 May 2001. In addition to the issues mentioned above, the working group shall assess how well the pharmaceutical services provided by institutions of out-patient care are functioning, and how the pharmaceutical sector is expected to develop internationally.

Collaboration is always necessary at preparatory stages and during the practical implementation of changes, and that applies also to the policy on pharmaceuticals. The best results – in this case the best possible medical therapy for Finnish patients, and through that a general improvement in their state of health – can be achieved by discussing the relevant issues, and taking into consideration different views.

Translation Liisa Fellman-Paul

Summary

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What information can be obtained by reports on adverse reactions?

The aim of pharmacovigilance is to maintain the level of drug safety by monitoring the risks involved in drug therapies and by deciding on any measures necessary. By compiling reports on adverse reactions it is possible to recognise new risks, which, as their extent is assessed in relation to the benefits, will finally result in well-founded measures promoting drug safety. The register of adverse reactions based on the compilation of individual reports on adverse reactions has remained the corner-stone of the entire exercise since the 1960's.

Could this register be used for anything more than detecting rare signals?

Would more widely based reporting practices reveal epidemiological quantitative information on adverse reactions?

The entire concept of adverse reactions is problematical not only in the philosophical sense, but in practice as well. People constantly experience various changes in their condition. Only a very few of the symptoms which we in everyday language call adverse reactions of drugs are such that they could occur solely in association with the use of a drug. In that respect we are mainly limited to confirmed immunological adverse effects associated with a specific antibody against a certain molecular structure. Usually, our conclusion that a drug has caused a change in a person's condition (an adverse effect) is based only on intuitive reasoning that the sequence of events in time would imply a causal connection *(post hoc, ergo propter hoc)*. Strictly speaking, generally there is no "direct" confirmation of a causal connection.

The causal connection which we imagine is not a simple matter of yes or no according to Aristotelian logic but rather it contains other alternatives in that it is a question of coincidence in time, through various contributory stages finally arriving at the statement that it was the drug that "caused" the event (e.g. erosion caused by a tablet stuck in the oesophagus, and even then you could suppose that the thickness of the oesophageal mucosa, differences in motility etc. would have some effect). It would be better to consider this phenomenon on the basis of fuzzy logic: then all changes in health are more or less part of adverse drug reactions, some almost 0% (especially if the individual has not even received the drug, but we don't generally know this for sure either) and some almost 100%. We don't get very far either with these conclusions in each individual case but the causal connection should be studied as a more general form of the expression of statistical probability.

The above conceptual problem will result in some interesting perspectives associated with the compilation of reports on adverse reactions:

♦ *It is impossible, even in theory, to know the exact number and frequency of adverse reactions and, therefore, under-reporting is actually an absurd concept. For example, studies which, on the basis of a systematic review of series of cases or patient records, aim to establish adverse drug reactions causing hospitalisation, whether they are carried out retrospectively or prospectively, only reveal the researchers' opinion based on general medical knowledge on the proportion of drugs as the cause of hospitalisation, i.e. nothing more than an educated guess in the scientific sense. Even at best, the result reflects the researchers' extent of knowledge, not the true frequency of adverse reactions.*

♦ *The more infrequently an adverse event occurs in the population, the better spontaneous reporting becomes as a means of detecting whether the risk is considerably increased by a certain drug. An example: a total of 10–12 cases of aplastic anaemia are diagnosed annually in Finland irrespective of cause. If in any year a suspicion arises of, say, three or four cases of aplastic anaemia in the users of drug A, and the number of users of this drug is, for example, 1% (50,000), then, based on such sparse information as this, we can conclude with fair probability that this particular drug increases the risk of aplastic anaemia.*

♦ *If, on the contrary, the adverse event under study is prevalent, all the information gained by reporting adverse reactions will become difficult to interpret. Another example: about 200,000 cases of gastrointestinal haemorrhage occure each year in Finland irrespective of cause. One year, say, a total of 8 cases of suspected haemorrhage is reported as being caused by drug A and the number of suspected cases reported as being caused by drug B is 1. The number of users of both drugs in Finland that year was 100,000. Can we say that A or B increases the risk of haemorrhage or that A is more dangerous than B? Of course we can't the reason being that, also quite coincidentally, the number of cases in user populations of this size may reach thousands. If we then consider that the issue will be settled if all cases are reported, the end result will also include, in addition to all the cases "caused by the drug", all those that were associated merely by chance.*

It should be borne in mind that, in principle, the conceptual controversy is associated with both prospective controlled clinical trials and non-experimental epidemiological studies. However, in these studies the problem is avoided by compiling information on all adverse events and then comparing these in the treated and control patients. We can then talk about causality if the study has been done prospectively but in the case of a non-experimental epidemiological study the issue remains much more uncertain.

In spite of the above problems we can say that the register of adverse reactions based on spontaneous reporting is important and is often in practice the only feasible means of discovering rare severe adverse reactions. However, it is very important to bear its limitations in mind and to understand at the same time that widening the area of application of this information compiling system to cover more general adverse events and abolishing the "under-reporting" will multiply the amount of information on which no conclusions can be drawn and which is easily misinterpreted. Quantitative information on adverse drug effects should generally be obtained through epidemiological studies.

Summary

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Hepatic reactions associated with the use of anti-inflammatory analgesics

Liver damage caused by anti-inflammatory analgesics is very rare. The incidence of symptomatic liver damage is estimated at 0.001–0.05%. Symptom-free, mild increase in hepatic enzymes is more common and may occur in as many as 5–15% of patients. The frequency and the pattern of liver damage vary between the anti-inflammatory analgesics. The damage is classified as hepatocellular, cholestatic or as a mixture of these. Hepatocellular damage is often associated with hepatocellular necrosis. The levels of hepatic enzymes (AST, ALT) are considerably increased, whereas the levels of serum alkaline phosphatase (ALP) and bilirubin are increased less. In the case of cholestatic damage the biliary secretion is decreased and the serum levels of ALP and bilirubin are increased. The increase in hepatic enzymes may be quite small. The prognosis of cholestatic damage is better than that of hepatocellular damage and the normal situation is often restored after withdrawal of medication. The diagnosis of hepatitis requires a histological lesion diagnosed with the aid of liver biopsy.

The mechanisms of liver damage caused by anti-inflammatory analgesics are not well known. The reactions may be idiosyncratic, host-dependent and lacking precise correlation with the dose. The damage may be caused by a reactive/toxic metabolite formed from the drug. Sometimes the liver damage may be associated with symptoms indicative of hypersensitivity reaction (e.g. fever, eosinophilia, rash, arthralgia).

The register of adverse reactions maintained by the National Agency for Medicines vas received a total of about 15,200 reports between 1973 and November 2000 on suspected adverse reactions in association with the use of drugs. About one thousand (6.6%) of these reports involved a variety of effects on the liver. A total of 59 cases have been reported in association with the use of anti-inflammatory analgesics where the patient's liver was found to have been adversely affected (Table). The majority of cases only involved a change in liver function tests.

Nimesulide

A total of 17 of the reports on adverse effects on the liver were linked with the use of nimesulide. Eight of these cases involved hepatitis and nine increased hepatic enzyme levels. The majority of patients (14) were women. The average age was 61 years (range between 23 and 88 years), and nine of the patients were over 60 years of age. The symptoms or findings of liver effects usually appeared after 1–6 weeks of treatment. In eleven patients' the laboratory values had returned to normal at the follow-up after nimesulide was stopped. Six patients had still not recovered 2–8 weeks after withdrawal of medication, when the report on the adverse effect was made. Five patients were using concomitant drugs which have been reported to have hepatic reactions. According to published case reports, nimesulide can cause both hepatocellular necrosis and pure cholestasis. Individual cases of fatal liver damage have also been reported.

Nimesulide is a relatively new

Hepatic reactions caused by anti-inflammatory analgesics and included in the register of adverse effects of the National Agency for Medicines during 1973–November 2000.

Drug	*Number*
Hepatitis	
nimesulide	*8*
diclofenac	*3*
naproxen	*2*
acetylsalicylic acid	*1*
ibuprofen	*1*
piroxicam	*1*
Other liver damage (no evidence of hepatitis)	
diflunisal	*1*
indomethacin	*1*
Increased hepatic enzymes	
nimesulide	*9*
diclofenac	*8*
ibuprofen	*5*
tolfenamic acid	*5*
indomethacin	*4*
ketoprofen	*2*
acetylsalicylic acid	*1*
phenylbutazone	*1*
mefenamic acid	*1*
meloxicam	*1*
naproxen	*1*
oxyphenbutazone	*1*
piroxicam	*1*
sulindac	*1*
tiaprofen acid	*1*

drug, introduced on the Finnish market in January 1998. It is widely used, however, and the number of daily doses (0.2 g) by September 2000 totalled over 14 million. One reason for the popularity of nimesulide is probably its selectivity which, as a COX-2 inhibitor, is claimed to be higher than that of older anti-inflammatory analgesics and the fewer cases of gastrointestinal tract ulcers it causes.

Due to its adverse effects on the liver, the product information on nimesulide was updated at the beginning of 2000. Hepatic insufficiency was added to the contraindications and additional text was included in the section on warnings according to which patients with abnormal values in their liver function tests and/or patients with symptoms indicative of liver damage (anorexia, nausea, vomiting, jaundice) during nimesulide therapy must be closely monitored and medication stopped. These patients should not be re-exposed to nimesulide. Increased hepatic enzyme values were included in rare adverse effects in the SPC, and cholestatis and rapidly developing hepatitis were included in the list of very rare adverse effects.

Diclofenac

Among anti-inflammatory analgesics, the second largest number of reports on adverse effects on the liver received by the register on adverse reactions is associated with the use of diclofenac (11 cases). The average age of the patients was 53 (varying between 31 and 80 years) and nine of the patients were women. According to the reports, liver values returned to normal in seven patients after withdrawal of medication and one case of liver damage proved fatal. Diclofenac has been in clinical use since 1977. The reports on adverse hepatic effects are distributed rather evenly in the years between 1978 and 2000. A hepatic reaction associated with diclofenac may not appear until after several months of treatment. The liver damage is usually of a hepatocellular or mixed type and less than 10 % of cases have features of cholestatic damage. Predisposition to the liver damage caused by diclofenac appears to increase with advancing age.

Other anti-inflammatory analgesics

According to the literature, the use of sulindac is associated with liver reactions. The drug is no longer available on the Finnish market. Hepatic reactions associated with other anti-inflammatory analgesics currently in use are very rare. This would appear to be true also according to the reports received by the register of adverse effects of the National Agency for Medicines (Table).

Conclusion

The risk of liver damage associated with anti-inflammatory analgesics is very small compared with the symptoms of gastric irritation, ulcer and gastrointestinal haemorrhage that they cause. Howerer, the risk of hepatic reactions caused by anti-inflammatory analgesics may increase with age. The risk of liver damage is also greater in patients on concomitant therapy with some other hepatotoxic medication. Patients with rheumatoid arthritis, for example, use many drugs which have been associated with liver damage. These include, for example, gold salts, sulphasalazine, penicillamine, methotrexate and ciclosporine. There is no information based on studies regarding underlying hepatic disorders or excess consumption of alcohol, but care should be exercised when treating these patients.

Translation Mervi Moisander